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ranking remaining positions of the molecule using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the positions of the molecule and selecting a top number n of positions; and

optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the molecule to vary.

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(Twice Amended) 30. The at least one program storage device of claim 29, wherein said optimizing comprises optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the molecule to vary.

Remarks

Claims 1-30 were originally filed with the present application, and are currently pending herein. All of the claims stand as rejected. Rejections of the claims are addressed separately below in the order raised in the outstanding Office Action, particularly in view of issues discussed during a telephone interview between Examiners Sheinberg and Marschel and Applicants' undersigned Attorney on March 1, 2002. A summary of the interview is hereby provided, as requested:

Rejections under 35 U.S.C. §112:

Regarding language in claims 1, 11, and 21 excluding assembly of two or more fragments from the claimed method, alternate language ("incremental construction") was proposed and accepted. Regarding the use of a Monte Carlo search algorithm, the Examiners suggested presenting a review of methods for generating random conformations if Applicants were to claim that the Monte Carlo algorithm is not essential. In the alternative, a standard work in the art should be cited to show that the method is well known. The rejection of claims 8, 18 and 28 was clarified as being due to an error in amending claims - the term 'vector' was

not included in amendments to claims 18 and 28. Regarding whether the claimed method is non-virtual/virtual, it was suggested that the term 'computer-implemented' be added to the preamble of claims 1 and 11 to clarify that the invention does not contemplate wet-chemistry methods.
Regarding the 'optimization' step in claims 9, 19, and 29, language to overcome the rejection was discussed.

Rejections under 35 U.S.C. §102

The Examiners clarified that their position is that the term 'ligand' in the claims could be construed as encompassing fragments of molecules, and, therefore, the claims read on the initial docking step of the Ho reference. Language to overcome the rejection was discussed.

Attached hereto is a marked up version of the changes made to claims 1, 4, 7, 9-11, 14, 17-21, 24 and 27-30. The attached page is captioned "**Version with markings to show changes made**." Entry of the amendments and new claims, and reconsideration of the application are respectfully requested. Rejections of the claims are addressed separately below in the order raised in the outstanding Office Action.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 11 and 21 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action states that the specification does not disclose any clear contemplation of not using broken fragments as docking ligands, and, thus, the amendments made to claims 1, 11 and 21 are considered new matter. Applicants respectfully disagree with this suggestion, and vigorously assert that the specification clearly distinguishes the claimed method over methods using molecular fragments to build up a ligand at the active site. However, in the interests of advancing prosecution, the

claims are now amended to recite alternative language that more clearly conveys this. Accordingly, the last line of claims 1 and 21 now read "wherein said method is not an incremental construction method," and the last line of claim 11 reads "wherein said system does not use an incremental construction method." Support for the amendment may be found in the specification on page 5, lines 7-31, page 6, line 9, page 10, line 25 through page 11 line 6 and page 27, lines 7-13.

In addition, the Office Action states that use of a Monte Carlo search algorithm appears critical or essential to the practice of the invention, but is not enabled by the disclosure. Such algorithms may be used in the methods of the present invention for generating random configurations of large molecules to be docked to the target, as noted in the specification on page 32; these are not typically used for small molecules. Monte Carlo simulation or search methods or algorithms are derived from the simulated annealing algorithm originally described by Metropolis *et al.* (Metropolis *et al.* J Chem. Phys. (1953) vol. 21, pg. 1087), and are well known in the art. A Monte Carlo search algorithm for generating random conformations typically works as follows: Initial molecular structures are randomly altered by generating simulated thermal perturbations. The generated perturbation typically must preserve all structural constraints and be energetically favorable. If both conditions are not met, the perturbation will be discarded. Because these methods/algorithms are well known in the art, Applicants respectfully submit that a detailed description thereof is not required. Use of a Monte Carlo algorithm is described in, for example, U.S. Patent No. 5,241,470 to Lee *et al.*; U.S. Patent No. 5,265,030 to Skolnick *et al.*; and U.S. Patent No. 6,341,256 to Deem *et al.*, and references cited therein. Scientific references describing use include Kirkpartick *et al.*, "Optimization by Simulated Annealing", Science 220 (1983) pp 671-680; and Wond and Liang, "Dynamic Weighting in Monte Carlo Optimization", Proc. Natl. Acad. Sci. USA 94 (1997) pp. 14220-14224. It is believed that the rejection is hereby overcome.

Claims 8, 18 and 28 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. As noted above, during the interview,

Examiner Sheinberg clarified that amendment to claim 8 had overcome the rejection, and that the current rejection related to the lack of appropriate amendments to claims 18 and 28 in the previous Response. This error has now been corrected, and claims 18 and 28 now recite the same language as claim 8. It is believed that the rejection is hereby overcome.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-30 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action states that claims 1, 11 and 21 are vague and indefinite in that the body of the claims does not perform what the preamble sets out to do, as the preamble sets forth a non-virtual method while the body of the claims recites a virtual or computer-implemented method. Claims 1 and 11 are now amended to recite a "computer-aided method" and "computer-aided system," respectively, in the preamble. As noted by Examiner Sheinberg during the interview, support for the amendment may be found in claims 21-30, which relate to computer systems and storage devices. It is believed that the rejection is hereby overcome.

Claim 10 is rejected as having insufficient antecedent basis for the limitation "said simple atom pairwise score". The claim is now amended to recite "said atom pairwise score". Claims 5,6, 15, 16, 25 and 16 are rejected as having insufficient antecedent basis for the term "the binding site". Claims 1, 11, and 21 are now amended to recite "a protein having a binding site" in line 1. Claims 9, 19 and 29 are rejected as lacking clarity in the number of optimization steps. It was pointed out during the interview that the method of claims 1, 11 and 21 is further limited in claims 9, 19 and 29 to cases where multiple positions of the molecule are obtained, and that the optimization step is further limited to ranking, clustering and optimizing the top n clustered positions. Claims 9, 19, and 29 are now amended to clarify this. Claims 8, 18 and 28 are rejected as lacking clarity regarding minimization. It is believed that the amendments to claims 18 and 28, discussed above, overcome the rejection.

Rejections Under 35 U.S.C. §102

Claims 1-30 are rejected under 35 U.S.C. §102(e) as being anticipated by Ho, *et al.* As noted above, during the interview, the Examiners explained their view that the term 'ligand' in the claims could be interpreted as encompassing the molecular fragments, such that the claims would read on the initial step of Ho's method, that is, placing a first molecular fragment into the site. Although, in the context of the present invention, the term ligand is used to refer to a complete or 'entire' chemical compound, it is acknowledged that, in some technology areas, for example, inorganic chemistry, the term can refer to a part of a chemical compound. Therefore, in order to more clearly distinguish the present invention over prior art methods, claims 1, 11 and 21 are amended to recite a 'molecule' rather than a 'ligand'. Support for the amendment may be found throughout the specification, beginning with the title. The term 'molecule' is defined by the *Academic Press Dictionary of Science and Technology*, edited by Christopher Morris, Academic Press (1992) as "the smallest unit of matter of a substance that retains all the physical and chemical properties of that substance, consisting of a single atom or a group of atoms bonded together." Applicants submit that the term 'molecule' would not be interpreted by any person of skill in the chemical arts as including fragments of chemical compounds, since these are not 'substances' having definite physical and chemical properties, but rather, as an entire, complete chemical compound. In addition, as discussed above, the claims also recite that the methods are not "an incremental construction method." Applicants submit that by these amendments, the claims are clearly distinguished over the reference. It is believed that the rejection is hereby overcome.

In view of the above Amendment and Remarks, Applicants respectfully request allowance of all claims pending herein. Should any questions arise in connection with this Application, Applicants' Attorney can be reached at the below-listed telephone number.

Respectfully submitted,

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Version with markings to show changes made

(Twice Amended) 1. A computer-aided method of docking a [ligand] molecule to a protein having a binding site, said method comprising:

performing a pre-docking conformational search to generate multiple solution conformations of the [ligand] molecule;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the [ligand] molecule to obtain at least one [ligand] position of the molecule relative to the protein in a [ligand-protein complex formation] protein-ligand complex; and

optimizing the at least one [ligand] position of the molecule while allowing translation, orientation and rotatable bonds of the [ligand] molecule to vary, and while holding the protein fixed;

wherein said method [does not involve assembly of two or more fragments to form the ligand] is not an incremental construction method.

(Twice Amended) 4. The method of claim 1, wherein said performing the pre-docking conformational search comprises:

randomly generating a plurality of conformations of the [ligand] molecule;

minimizing a strain of each conformation of the plurality of conformations;

using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of [top] clusters of conformations, said retained top number of [top] clusters of conformations comprising said multiple solution conformations of the [ligand] molecule.

(Amended) 7. The method of claim 1, wherein said matching comprises:

matching atoms of the at least one solution conformation to appropriate hot spots of the protein by positioning the at least one solution conformation as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one solution conformation of the [ligand] molecule into the binding site of the protein.

(Twice Amended) 9. The method of claim 1, wherein [said optimizing comprises optimizing] multiple [protein-ligand complex formations] positions of the molecule are obtained, and said optimizing [comprising] step comprises :

eliminating each [ligand] position of the molecule having a predetermined percentage of [ligand] atoms with a steric clash;

ranking remaining [ligand] positions of the molecule using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the [ligand] positions of the molecule and selecting a top number n of [ligand] positions; and

optimizing each [ligand position] of the n positions, allowing the translation, [rotation] orientation and rotatable bonds of the [ligand] molecule to vary.

(Twice Amended) 10. The method of claim 9, wherein said optimizing comprises optimizing each [ligand] position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said [simple] atom pairwise score, allowing the translation, [rotation] orientation and rotatable bonds of the [ligand] molecule to vary.

(Twice Amended) 11. A computer-aided system for docking a [ligand] molecule to a protein having a binding site, said system comprising:

means for performing a pre-docking conformational search to generate multiple solution conformations of the [ligand] molecule;

means for generating a binding site image of the protein, said binding site image comprising multiple hot spots;

means for matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the [ligand] molecule to

obtain at least one [ligand] position of the molecule relative to the protein in a [ligand-protein complex formation] protein-ligand complex; and

means for optimizing the at least one [ligand] position of the molecule while allowing translation, orientation and rotatable bonds of the [ligand] molecule to vary, and while holding the protein fixed;

wherein said [method does not involve assembly of two or more fragments to form the ligand] system does not use an incremental construction method.

(Twice Amended) 14. The system of claim 11, wherein said means for performing the pre-docking conformational search comprises:

means for randomly generating a plurality of conformations of the [ligand] molecule;

means for minimizing a strain of each conformation of the plurality of conformations;

means for using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

means for clustering the conformations and retaining a desired top number of [top] clusters of conformations, said retained top number of [top] clusters of conformations comprising said multiple solution conformations of the [ligand] molecule.

(Amended) 17. The system of claim 11, wherein said means for matching comprises:

means for matching atoms of the at least one solution conformation to appropriate hot spots of the protein by positioning the at least one solution conformation as a rigid body into the binding site image;

means for defining a match, said match determining a unique rigid body transformation; and

means for using the unique rigid body transformation to place the at least one solution conformation of the [ligand] molecule into the binding site of the protein.

(Twice Amended) 18. The system of claim 17, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R, T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

I(R,T) = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one solution conformation;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one solution conformation;

R = a 3×3 rotation matrix; and

T = a translation vector.

(Twice Amended) 19. The system of claim 11, wherein [said means for optimizing comprises means for optimizing] multiple [protein-ligand complex formations] positions of the molecule are obtained, and said means for optimizing [comprising] comprises:

means for eliminating each [ligand] position of the molecule having a predetermined percentage of [ligand] atoms with a steric clash;

means for ranking remaining [ligand] positions of the molecule using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, means for clustering the [ligand] positions of the molecule and selecting a top number n of [ligand] positions; and

means for optimizing each [ligand position] of the n positions, allowing the translation, [rotation] orientation and rotatable bonds of the [ligand] molecule to vary.

(Twice Amended) 20. The system of claim 19, wherein said means for optimizing comprises means for optimizing each [ligand] position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with [a simple] said atom pairwise score, allowing the translation, [rotation] orientation and rotatable bonds of the [ligand] molecule to vary.

(Twice Amended) 21. At least one program storage device readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of docking a [ligand] molecule to a protein having a binding site, said method, comprising:

performing a pre-docking conformational search to generate multiple solution conformations of the [ligand] molecule;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the [ligand] molecule to obtain at least one [ligand] position of the molecule relative to the protein in a protein-ligand complex; and

optimizing the at least one [ligand] position while allowing translation, orientation and rotatable bonds of the [ligand] molecule to vary, and while holding the protein fixed ; wherein said method [does not involve assembly of two or more fragments to form the ligand] is not an incremental construction method.

(Twice Amended) 24. The at least one program storage device of claim 21, wherein said performing the pre-docking conformational search comprises:

randomly generating a plurality of conformations of the [ligand] molecule;

minimizing a strain and a solvent accessible surface area of each conformation of the plurality of conformations;

using the strain of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of [top] clusters of conformations, said retained top number of [top] clusters of conformations comprising said multiple solution conformations of the [ligand] molecule.

(Amended) 27. The at least one program storage device of claim 21, wherein said matching comprises:

matching atoms of the at least one solution conformation to appropriate hot spots of the protein by positioning the at least one solution conformation as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one solution conformation of the [ligand] molecule into the binding site of the protein.

(Twice Amended) 28. The at least one program storage device of claim 27, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R, T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

$I(R,T)$ = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one solution conformation;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one solution conformation;

R = a 3×3 rotation matrix; and

T = a translation vector.

(Twice Amended) 29. The at least one program storage device of claim 21, wherein [said optimizing comprises optimizing] multiple [protein-ligand complex formations] positions of the molecule are obtained, and said optimizing [comprising] step comprises :

eliminating each [ligand] position of the molecule having a predetermined percentage of [ligand] atoms with a steric clash;

ranking remaining [ligand] positions of the molecule using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the [ligand] positions of the molecule and selecting a top number n of [ligand] positions; and

optimizing each [ligand position] of the n positions, allowing the translation, [rotation] orientation and rotatable bonds of the [ligand] molecule to vary.

(Twice Amended) 30. The at least one program storage device of claim 29, wherein said optimizing comprises optimizing each [ligand] position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with [a simple] said atom pairwise score, allowing the translation, [rotation] orientation and rotatable bonds of the [ligand] molecule to vary.